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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/695,446	10/24/2000	Suzana Petanceska	0630/1G184-US1	2608

32801 7590 06/11/2007
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EXAMINER
KISHORE, GOLLAMUDI S

ART UNIT	PAPER NUMBER
1615	

MAIL DATE	DELIVERY MODE
06/11/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/695,446	PETANCESKA ET AL.	
	Examiner	Art Unit	
	Gollamudi S. Kishore, Ph.D	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,20,22-24,31,34 and 35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,20,22-24,31,34 and 35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The RCE dated 3-30-07 is acknowledged.

Claims included in the prosecution are 1-6, 20, 22-24, 31 and 34-35.

In view of the amendment to claim 1, the 112, 1st paragraph rejection is withdrawn. Previous 102 rejections over Simpkin, and Washburn are also withdrawn.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1-6, 20, 22-24, 31 and 34-35 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is unclear as to which organ or cell is being referred to where the level of amyloid beta peptides are reduced without affecting the soluble APP levels. If 'estradiol' is the compound, then reciting 'compound' in addition is redundant. The examiner suggests the deletion of the term, 'compound'.

'at least one symptom associated with Alzheimer's disease' renders claim 24 indefinite. The examiner suggests reciting the symptoms.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 1-3, 5-6, 24, 31 and 34-35 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 98/43647 of record.

Instant claims are drawn to a method of reducing the level of amyloid-beta peptides in vivo without increasing the levels of A beta by the administration of either estradiol or conjugated equine estrogen in a A beta level reducing dose. The dependent claims define the effective amounts as 0.5 micrograms to 50 mg.

WO teaches administration of 17 beta-estradiol at dosages of 0.01 to 25 mg/Kg body weight, in particular, a single dosage of 1, 5 and 10 mg for the reduction of APP fragments which include A beta (abstract, page 14, lines 6-13. WO further teaches methods for alleviating an impaired condition brought on by neurodegenerative or cognitive changes (claim 22). The formulations include controlled release formulations (page 15, lines 16-23). Since the dosages taught by WO are the same as in instant invention, the effect of the estrogen compound on sAPP levels and the ratios of A beta peptides would be the same.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that WO does not disclose methods for lowering A beta levels without affecting s APP levels. According to applicant, WO discloses a method of treating neurodegenerative disorders by reducing APP holoprotein expression levels and APP mRNA synthesis through administration of estrogenic compounds such as

estradiol. This argument is not persuasive since WO teaches the reduction of APP fragments and not just holoprotein. The reduction of A beta peptides thus, implicit. Furthermore, since the prior art administers the same compound in same amounts, the claimed reduction of the A beta peptides without affecting sAPP levels is inherent in WO. In addition, as pointed out in the previous action, a careful examination of Fig. 3 in the specification indicates no changes in soluble APP levels in intact animals, animals deprived of the physiological levels of estrogens and estrogen administered at 1 mg and 5 mg dosages. This shows that estrogen at any dosage level does not affect the s APP levels. Therefore, one would not expect any increase in the sAPP levels after the administration of 1, 5 and 10 mg of estradiol as taught by WO.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claim 1-6, 20, 22-24, 31 and 34-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 98/43647 of record.

WO as pointed out above teaches administration of 17 beta-estradiol at dosages of 0.01 to 25 mg/Kg body weight, in particular, a single dosage of 1, 5 and 10 mg for the reduction of APP fragments which include A beta (abstract, page 14, lines 6-13. WO further teaches methods for alleviating an impaired condition brought on by neurodegenerative or cognitive changes (claim 22). The formulations include controlled

release formulations (page 15, lines 16-23). Although WO does not explicitly teach the reduction of the level of amyloid-beta peptides, since it teaches the reduction of APP and its fragments, it would have been obvious to one of ordinary skill in the art that even the amyloid-beta peptide is reduced since APP is the precursor for this peptide. Since the dosages taught by WO are the same as in instant invention, the effect of the estrogen compound on sAPP levels and the ratios of A beta peptides would be the same. Although WO does not teach the administration of the compound for at least 10 days, protocol of administration is deemed to be an obvious parameter manipulated by an artisan.

7. Claim 1-2, 5-6, 24 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 98/43647 of record in view of Washburn (5,719,137).

Washburn discloses the effectiveness of 7 alpha dihydroequilenin and compares it with estradiol in a method of reducing the risk of Alzheimer's disease and the method of treating other dementia related conditions in males and females. The composition is administered in a transdermal patch (control release) (abstract, col. 3, lines 22-60, col. 8, lines 2-3, examples and claims).

Simpkins teaches the neuroprotective effect and treatment of the neurodegenerative disorder, Alzheimer's disease by administering 17-b-estradiol and conjugated estrogen. The composition is either administered daily or by a control release device (abstract, col. 10, lines 4-19 and 26-33, Example 3b on col. 17 and claims).

The use of a conjugated estrogen instead of estradiol taught by WO would have been obvious to one of ordinary skill in the art with a reasonable expectation of success since Simpkins, and Washburn both teach the equivalency between these two compounds (col. 4, lines 50-61 and Table II).

8. Claims 1-6, 20, 22-24, 31 and 34-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/48488 in combination with Washburn (5,510,342), Holland (3,843,662) or Lundeen (Endocrinology, vol. 138, pp. 1552, 1997) individually or taken together.

WO teaches that blood cholesterol levels correlate with the production of amyloid protein and are predictors of populations at risk of developing Alzheimer's disease (AD). According to WO, methods of lowering cholesterol can be used to decrease production of A beta, thereby decreasing the risk of developing AD (abstract, pages 1-6, Example 3 and claims). What is lacking in WO is the use of estrogens.

Washburn discloses that estrogens and conjugated estrogens lower blood cholesterol (table 1 on col. 4; col. 7, line 67 through col. 8, line 22).

Holland teaches that lowering of blood cholesterol by estrogens is known (col. 1, lines 25-28).

Lundeen similarly teaches that estrogens (estradiol and ethinyl estradiol) reduce plasma cholesterol levels (abstract, Results and Discussion).

It would have been obvious to one of ordinary skill in the art to use estrogens in the teaching of WO, that is, for lowering the levels of A beta peptide and decrease the

risk of developing Alzheimer's disease since Washburn, Holland, and Lundeen teach that estrogens and conjugated estrogens lower cholesterol and because WO teaches that methods of lowering cholesterol can be used to decrease production of A beta, thereby decreasing the risk of developing AD. In the absence of showing the criticality, instant doses and protocol of administration are deemed to be obvious parameters manipulated by an artisan since these depend upon the severity of the condition and the age of the patient.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant's arguments once again are based on the lack of dosage amounts in the prior art. These have been addressed above.
Furthermore, as pointed out in the previous action, WO clearly establishes the correlation between cholesterol levels, amyloid proteins and Alzheimer's disease and shows the effect of cholesterol lowering compounds in lowering the production of A beta thereby decreasing the risk of developing AD. Therefore, instant method would have been obvious to one of ordinary skill in the art based on the combined teachings of WO, Washburn, Holland or Lundeen. Furthermore, as pointed out above, a careful examination of Fig. 3 in the specification indicates no changes in soluble APP levels in intact animals, animals deprived of the physiological levels of estrogens and estrogen administered at 1 mg and 5 mg dosages. This shows that estrogen at any dosage level does not affect the s APP levels. Applicant's arguments based on Fagan et al's reference which apparently show no differences in the A beta pathology in PDAPP mice of various apo AI genotypes despite robust differences in plasma cholesterol levels

between the groups are not persuasive. WO teachings are based on human neuronal cultures whereas Fagan et al's study is based on rat model. This shows that the results vary with different models and one would expect the same with applicant's studies; instant claims however, are drawn to 'animals' in general which includes human males and females and 'generic' estrogen compounds. Since WO's teachings are based on human neurons, it would be obvious to one of ordinary skill in the art that the results can be extrapolated to in vivo administration to humans with a reasonable expectation of success. As pointed out before, instant specification neither shows no unexpected results in terms of treating the diseases claimed nor establishes the criticality of the soluble APP levels.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S. Kishore, Ph.D whose telephone number is (571) 272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Woodward Michael can be reached on (571) 272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/ S Kishore

Gollamudi S Kishore, Ph.D
Primary Examiner
Art Unit 1615

GSK